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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,612	07/27/2000	James C. Liao	06497-013001	9658

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EXAMINER
PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/06/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/626,612	Liao
Examiner	**Art Unit**
Rebecca Prouty	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 6-25-02 and 8-14-02 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-35 is/are pending in the application.

4a) Of the above, claim(s) 8-23 and 25-35 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-7 and 24 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election without traverse of Group I, Claims 1-21, and 24-35 in Paper No. 7 is acknowledged.

Applicant's election without traverse of *glnAp2* as promoter and phosphoenolpyruvate synthase (pps) as heterologous polypeptide in Paper No. 9 is acknowledged.

Claims 8-23 and 25-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (Claims 22 and 23) or species (Claims 8-21 and 25-35), there being no allowable generic or linking claim. Note Claims 8-21 and 25-35 are not drawn to the elected species of heterologous polypeptide as pps is not a required enzyme for the biosynthesis of any metabolite. The product of the reaction catalyzed by pps, (i.e., PEP) can be provided to the cell by many other routes of synthesis making pps activity non-essential to the synthesis of metabolites which are produced using PEP as a precursor. Election was made without traverse in Paper Nos. 7 and 9.

Claims 1-7 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of bacterial host cells or kits comprising said host cells wherein the host cells comprise any promoter which is controlled by any response regulator protein/heterologous polypeptide construct and any genetic modification that makes the promoter regulated by acetyl phosphate. The specification teaches the only the five representative species of *E. coli* strains JCL1596, BW18302(*glnAp2-aroG*), BW18302(*glnAp2-pps*), BW18302(p2IDI), and BW18302(p2IDI/pPSG184) all of which utilize the same bacterial host cell with the same genetic modification (*E. coli* having a *glnL* mutation) and the same promoter which is regulated by the same response regulator(*glnAp2* which is regulated by *ntrC*). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-7 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *E.*

coli having a *glnL* mutation which are transformed with a nucleic acid encoding a heterologous polypeptide operably linked the *glnAp2* promoter or kits comprising an *E. coli* having a *glnL* mutation and a nucleic acid encoding the *glnAp2* promoter, does not reasonably provide enablement for any host cell wherein the host cell comprises any promoter which is controlled by any response regulator protein/heterologous polypeptide construct and any genetic modification that makes the promoter regulated by acetyl phosphate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

These claims are so broad as to encompass any bacterial host cell or kits comprising said host cells wherein the host cells comprise any promoter which is controlled by any response regulator protein/heterologous polypeptide construct and any genetic modification that makes the promoter regulated by acetyl phosphate. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of promoters, regulatory proteins and genetic modifications of the host broadly encompassed by the claims. The amino acid sequence of a protein determines its

structural and functional properties and likewise the nucleotide sequence of a promoter determines its properties. Thus, predictability of which promoters, regulatory proteins and genetic modifications within a bacterial host can be tolerated and still have the desired ability to regulate function in response to a particular compound, requires a knowledge of and guidance with regard to (i) which promoters are regulated by what proteins, (ii) which amino acids/nucleotides in the sequence of the promoters and regulatory proteins are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), (iii) a detailed knowledge of the ways in which each promoter/regulatory proteins' structure relates to its ability to regulate transcription and (iv) how the structure and function of each of these is influenced and modified by potential modifications of the cell in which it occurs. However, in this case the disclosure is limited to the use of *E. coli* strains JCL1596, BW18302(*glnAp2-aroG*), BW18302(*glnAp2-pps*), BW18302(p2IDI), and BW18302(p2IDI/pPSG184) all of which utilize the same bacterial host cell with the same genetic modification (*E. coli* having a *glnL* mutation) and the same promoter which is regulated by the same response regulator (*glnAp2* which is regulated by *ntrC*).

The specification does not support the broad scope of Claims 1-7, and 24, because the specification does not establish: (A) the identity of promoters, regulatory proteins and genetic modifications within a bacterial host that have the desired ability to regulate function in response to a acetyl phosphate; (B) regions of any promoter/regulatory protein pair which may be modified without effecting the activity of said promoter to activate transcription in response to the regulatory protein and how the activity of any promoter/regulatory protein pair is influenced by the genetic modification of the host cell itself; (C) the general tolerance of the activities of said promoter/regulatory proteins to modification and extent of such tolerance; (D) a rational and predictable scheme for choosing which promoter/regulatory proteins to screen for the recited utilities and what types of bacterial cell modifications will produced the desired effects of the alteration of these functions; (E) a rational and predictable scheme for modifying any gene of any bacteria with an expectation of obtaining the desired biological function; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices of promoters, regulatory proteins and genetic modifications within a bacterial host is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any host cell comprising any promoter which is controlled by any response regulator protein/heterologous polypeptide construct and any genetic modification that makes the promoter regulated by acetyl phosphate. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of bacterial cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Farmer et al.

Farmer et al. teach the *E. coli* strains JCL1596, BW18302(*glnAp2-aroG*), BW18302(*glnAp2-pps*), BW18302(p2IDI), and BW18302(p2IDI/pPSG184) which comprises a nucleic acid encoding a *glnAp2* promoter operably linked to a *lacZ* gene (which encodes β-galactosidase), an *aroG* (which encodes DAHP synthase), a *pps* gene or an *idi* gene (which encodes isopentenyl diphosphate isomerase) and comprising *glnL* mutations such that the *glnAp2* promoter is regulated by acetyl phosphate. These strains anticipate Claims 1-7.

Claims 1, 2, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Haldiman et al. (Reference AQ of applicant's PTO-1449).

Haldiman et al. teach an *E. coli* strain BW24386 which comprises a nucleic acid encoding a *vanH* promoter operably linked to a *lacZ* gene (which encodes β-galactosidase) and comprising *ackA*, Δ*phoR*, and Δ*creC* mutations such that the *vanH* promoter is regulated by acetyl phosphate. This strain anticipates Claims 1, 2, and 6.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liao (WO96/08567) in view of Bock et al. (US Patent 5,830,692), McCleary et al. (Reference AK of applicant's PTO-1449), McCleary et al. (Reference AP of applicant's PTO-1449) and Haldiman et al. (Reference AQ of applicant's PTO-1449) or Feng et al. (Reference AL of applicant's PTO-1449).

Liao teach constructs for the recombinant expression of phosphoenol pyruvate synthase (pps) in cells producing aromatic metabolites and that the increased expression of pps is useful for increasing the amount of carbon flow into the aromatic pathway by producing increased amounts of DAHP. The constructs of Liao comprise the pps gene under the control of an inducible promoter. (see pages 18-19). Liao further shows that cells lacking induction of the pps gene produce significant amounts of the fermentation byproduct acetate indicating significant flux away from PEP and the aromatic pathway (see pages 22-23) but that

induction of the pps gene produces undetectable levels of acetate in the cells and near theoretical yields of DAHP.

Bock teach that inducible promoters such as lac, tac, and trp promoters possess several disadvantages in relation to their use for industrial production. These are that the repressors and inducers necessary for use of these promoters are expensive and difficult to handle, particularly when they are metabolizable substances (such as lactose and tryptophan), and cannot be induced completely when the repressor is present in molar excess. (see columns 1-2).

McCleary (AK) and McCleary (AP) teach that acetyl phosphate may act a global regulatory signal in *E. coli* responsible for the activation of a wide range or response regulators of two-component systems, including the *glnAp2* promoter, in the absence of their cognate histidine kinase (i.e., the *ntrB* gene product in the case of *glnAp2*). They further teach that acetyl-phosphate levels in bacteria correlate with the amount of acetate produced.

Haldiman et al. and Feng et al. each teach *E. coli* two-component system promoters (the *VanH* promoter in Haldiman et al. and the *glnAp2* promoter in Feng et al.) which are activated by a response regulator protein (*VanR* in Haldiman et al. and *NtrC* in Feng et al.) and acetyl phosphate in the absence of the

corresponding histidine kinases (*VanS* in Haldiman et al. and *NtrB* in Feng et al.) and in the presence or absence of nitrogen.

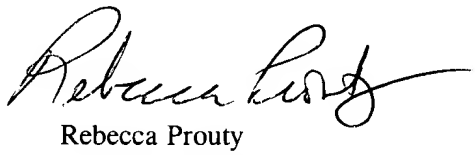
As inducers (IPTG) for promoters such as *tac* used by Liao are expensive and have disadvantages as taught by Bock, it would have been obvious to one of ordinary skill in the art to link the production of pps to the presence of a metabolite in the cell which signals that significant amounts of carbon are being diverted away from the aromatic biosynthetic pathway. Liao teach that acetate production occurs under these conditions. Therefore, it would have been obvious to one of ordinary skill in the art to replace the *tac* promoters in the constructs of Liao with a promoter which is induced by high acetate levels. As McCleary et al. (AK and AP) teach that acetyl-phosphate levels correlate with the amount of acetate produced, it would have been obvious to one of ordinary skill in the art to link the pps gene to the acetyl-phosphate regulated promoters taught by Haldiman et al. or Feng et al. and express these constructs in *E. coli* cells which lack the cognate histidine kinases such that the response regulators which activate transcription from these promoters are activated by acetyl phosphate. Furthermore, it would have been obvious to one of ordinary skill in the art to but the cells and

vectors necessary for production or high levels of aromatic metabolites together in a kit for easy handling.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Rebecca Prouty
Primary Examiner
Art Unit 1652